

herein, Applicants believe the rejection under 35 U.S.C. § 103(a) has been overcome. Reconsideration is respectfully requested.

I. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-5, 8, 13, 16-19 and 22 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Chemical Abstracts 99:172078 ("*Chem. Abstracts*"). According to the Office Action, it would have been *prima facie* obvious to one of skill in the art to arrive at the present invention by combining the teachings of *Chem. Abstracts* with common knowledge. In response, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143,

[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicants state that there is simply no motivation or suggestion provided in the cited reference to modify its teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 4 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The present invention relates to methods for administering low doses of nitric oxide mimetics to cells to inhibit and prevent a malignant cell phenotype. The

nitric oxide mimetics of the present invention are administered at such low doses that there is no appreciable effect on blood flows. For example, the Examiner's attention is respectfully directed to page 10, at the bottom, bridging to page 11, at the top, wherein it states:

In contrast, preferred doses of nitric oxide mimetic administered in the present invention to inhibit and prevent a malignant cell phenotype are lower, preferably at least 3 to 10,000-fold lower, more preferably at least 100- to at least 10,000-fold lower than those typically used in other therapeutic applications such as vasodilation and thus do not induce tolerance to the NO mimetic as quickly nor undesirable side effects.

Thus, the methods of the subject application administer NO mimetics at such low doses that blood flow is not appreciably effected.

In the Office Action, the Examiner acknowledges that the cited reference does *not* disclose that GTN administration would have the effect of inhibiting and preventing a malignant cell phenotype (*see*, page 3 of the Office Action). According to the Office Action, an agent that reduces tumor blood flow (such as nitroglycerin) would inhibit and prevent a malignant cell phenotype. The Examiner states:

Cancer cells need blood flow to survive and reduced blood flow would necessarily exhibit all such effects, essentially because the administration of the same exact GTN as taught by the cited reference cannot avoid such necessary end result, which is now claimed by Applicant.

Contrary to what is stated in the Office Action, it is well known in the art that tumor hypoxia (a deficiency in the amount of oxygen reaching body tissues) is associated with *increased* chemoresistance and radioresistance, and is predisposing for increased tumor metastases. In fact, hypoxia is known to accelerate malignant progression and increase metastasis.¹ As such, one of ordinary skill in the art would conclude that reducing blood flow would result in an *increase* in the apparent tumor cell

¹ Brown, The Hypoxic Cell: A Target for Selective Cancer Therapy *Cancer Research*, 1999, 59 (23) 5863-5870 (copy enclosed)

hypoxic fraction. Therefore, based on common knowledge, it would be undesirable to use GTN to treat cancer, as it was commonly believed that tumor hypoxia results in **greater** resistance to chemotherapy and radiation treatment, and leads to metastases.

According to M.P.E.P. § 2145,

[t]he totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Prior to the advent of the present invention, it was accepted wisdom that tumor hypoxia results in **greater** resistance to chemotherapy and radiation treatment. Thus, using GTN to treat cancer is proceeding against accepted wisdom and is therefore, strong evidence of nonobviousness. It is especially nonobvious to use such low doses of nitric oxide mimetics as are presently taught and claimed.

The Examiner's attention is respectfully directed to Table I on page 1322, of the full article (enclosed), which corresponds to *Chem. Abstracts*. As set forth therein, the effects of GTN on tumor blood flow as evidenced with the blood flow ratio (3rd column) is negligible. The blood flow ratio was 0.88 ± 0.20 for 15 minutes and 0.88 ± 0.13 for 30 minutes. Since the error limits are within the boundaries of no change in blood flow, the data arguably shows no decreased blood flow with administration of nitroglycerine. Given this data, Applicants assert that nitroglycerine would be the least likely candidate to be used to treat cancer.

Further, the Examiner's attention is respectfully directed to page 1323, right column, first paragraph of the enclosed full reference, wherein it states:

The present results demonstrate that pretreatment with either urethane or pentobarbital results in a three-fold **increase** in tumor cell survival following radiation. [Emphasis added].

Further on page 1324, on the right hand side it states:

The data indicate that an overall reduction in blood flow can be expected to **decrease** tumor radiosensitivity. [Emphasis added].

Since hypoxia results in greater resistance to chemotherapy, radiation treatment and increase in tumor cell survival, the cited reference actually teaches away from the present invention. As such, a skilled person would not be motivated to use a nitric oxide mimetic to treat cancer as is presently taught and claimed.

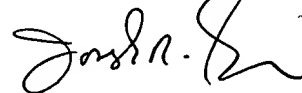
In view of the foregoing, Applicants assert that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the rejection be withdrawn.

II. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
JS/slw:sea
WC 9053421 v1